933,507

PATENT SPECIFICATION

NO DRAWINGS

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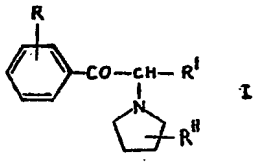
COMPLETE SPECIFICATION

α-Pyrrolidino-Ketones

We, Dr. KARL THOMAE, GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG, a German Body Corporate of Biberach an der Riss, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to therapeutically active α-pyrrolidino ketones and a process for the preparation thereof.

According to the invention, there are provided α-pyrrolidino ketones of the general formula



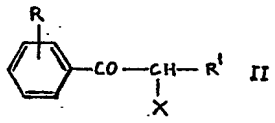
I

(in which R represents a hydrogen atom, an alkyl or alkoxy group each containing 1 to 3 carbon atoms, a hydroxyl group or a halogen atom, R^1 represents an alkyl group containing two to eight carbon atoms and R^{11} represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms) and non-toxic acid addition salts thereof.

Particularly preferred compounds according to the invention are 1 - phenyl - 2 - pyrrolidino - butanone - (1), 1 - phenyl - 2 - pyrrolidino - pentanone - (1), 1 - phenyl - 2 - pyrrolidino - hexanone - (1), 1 - (4^1 - methyl - phenyl) - 2 - pyrrolidino - pentanone - (1), 1 - (4^1 - hydroxy - phenyl) - 2 - pyrrolidino - pentanone - (1) and 1 - (3^1 - methyl - phenyl) - 2 - pyrrolidino - pentanone - (1).

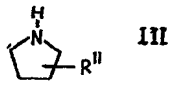
The compounds according to the invention may be prepared by any convenient method, for example by the following processes which constitute a further feature of the invention.

An α-halogeno ketone of the general formula



II

(in which R and R^1 have the meanings given above and X represents a halogen atom) is reacted with a pyrrolidine of the general formula



III

(in which R^{11} has the meaning given above). The reaction is preferably carried out in the presence of an inert organic solvent, such as, for example, benzene, toluene ether, acetone, carbon tetrachloride or chloroform, advantageously in the presence of an acid binding agent, such as an organic or inorganic base, for example, pyridine, quinoline or an N-dialkylaniline or an alkali or alkaline earth metal carbonate or bicarbonate e.g. sodium bicarbonate or potassium carbonate. An excess of the pyrrolidine of general formula III may also be conveniently used as acid binding agent. The reaction may advantageously be carried out at ambient or elevated temperatures.

Compounds of the general formula I in which R represents a hydroxyl group may be prepared from the corresponding compounds of general formula I in which R represents an alkoxy group.

Non-toxic acid addition salts of the compounds according to the invention may be formed with inorganic or organic acids, for example, hydrochloric, sulphuric, phosphoric,

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hydrobromic, methanesulphonic, tartaric, maleic, citric or phthalic acid.

α-Halogeno ketones of general formula II used as starting materials may be prepared by any convenient method, e.g. by bromination of the corresponding ketones in glacial acetic acid according to Schmidt, Ber. dtsch. Chem. Ges. Volume 22, Page 3251 (1889).

The compounds according to the invention have low toxicity and a marked therapeutic activity, having a pronounced stimulating effect on the central nervous system. Thus, for example, 1 - phenyl - 2 - pyrrolidino - pentanone - (1) - hydrochloride, 1 - (4^1 - methyl - phenyl) - 2 - pyrrolidino - pentanone - (1) - hydrochloride, 1 - phenyl - 2 - pyrrolidino - butanone - (1) - hydrochloride and 1 - (3^1 - methyl - phenyl) - 2 - pyrrolidino - pentanone - (1) - hydrochloride have all been found to possess a stimulating action on the central nervous system markedly greater than that of the corresponding 2-piperidino compounds. Some of the compounds, notably 1 - phenyl - 2 - pyrrolidino - pentanone - (1) - hydrochloride also possesses useful hypertensive and spasmolytic activity.

The compounds according to the invention may be formulated with an inert pharmaceutical carrier or excipient, for example, in compositions for oral or parenteral administration, advantageously in the form of dosage units. Each dosage unit preferably contains between 5 and 40 mg. of active substance, advantageously between 10 and 30 mg.

Compositions of oral administrations may take the form of tablets, capsules, dragees and like formulations, which contain the active substance together with a carrier, for example, lactose, glucose, talc, starch or kaolin, a binder, for example, stearic or alginic acid, carboxymethyl cellulose or pectin or, if desired, flavouring or sweetening agents.

Liquid compositions for oral administration may, for example, take the form of solutions, suspensions, syrups, elixirs, emulsions or drops, which contain the active substance together with a diluent, such as water, glycerol or ethanol, and, if desired, sweetening and/or flavouring agents.

Compositions for parenteral administration may take the form of ampoules, which contain the active substance together with a parenterally acceptable carrier, such as pyrogen-free water or an oil, e.g. olive oil or arachis oil.

In order that the invention may be well understood the following examples are given by way of illustration only:—

Example 1

α-Pyrrolidino-valerophenone

(a) 19.2 g. of α-bromovalerophenone ($B.pt._1 = 115°C.$) dissolved in 40 ml. of benzene at about 40°C. are added dropwise with stirring to 11.2 g. of pyrrolidine in 40 ml. benzene and the mixture stirred for a further 30 minutes. After standing for several hours, the solvent is evaporated in vacuo, the residue is taken up in dilute hydrochloric acid, shaken twice with ether and the acid aqueous solution made alkaline with sodium hydroxide solution. The amino ketone which separates is taken up in ether, and the solvent removed after drying over sodium sulphate. The crude product is distilled in vacuo yielding 18 g. of α - pyrrolidino - valerophenone, $B.pt._{0.15} = 113°C.$

The hydrochloride is prepared by dissolving the aminoketone in ether and adding ethereal hydrochloric acid. The crude hydrochloride is recrystallised from acetone-colourless crystals, m.p. 162°C. The following salts were also prepared:—acid sulphate, m.pt. = 140°C. (from isopropanol), maleate, m.pt. = 131°C. (from acetone), tartrate, m.pt. = 148—149°C. (from isopropanol) and citrate, m.pt. = 88°C. (decomp.) (from acetone).

(b) A solution of 24 g. of α - bromovalerophenone in 50 ml. carbon tetrachloride is added dropwise with stirring to 15 g. of pyrrolidine. The temperature is allowed to rise to 40°C. and stirring is continued for a 4 further hours. Further purification is effected as described under (a).

Yield: 20 g. of α-pyrrolidino-valerophenone, $b.pt._{0.2} = 116°C.$

(c) 24 g. of α - bromovalerophenone in 50 ml. of chloroform are added dropwise with stirring to 8 g. of pyrrolidine and 9 g. of sodium bicarbonate in 25 ml. of chloroform. After stirring for two hours and standing overnight, the product is purified as described under (a). The yield of α-pyrrolidino valerophenone is 16 g. The same product is obtained using acetone as solvent.

(d) 4 g. of pyrrolidine and 5 g. of pyridine in 20 ml. of ether are slowly added with continuous stirring to 12 g. of α-bromovalerophenone in 30 ml. of ether. Stirring is continuous for a further two hours and the product purified as described under (a). The yield of α - pyrrolidino - valerophenone is 7 g.

Example 2

1 - (4^1 - Methyl - phenyl) - 2 - pyrrolidino - pentanone - (1)

28.6 g. of pyrrolidine in 100 ml. of benzene are added dropwise to 25.6 g. of 1 - (4^1 - methyl - phenyl) - 2 - bromo - pentanone - (1) ($b.pt._{0.03} = 87—88°C.$) in 80 ml. benzene at 35—40°C. and stirring is continued for 5 hours at room temperature. The product is purified as described under Example 1(a).

Yield: 20 g., $b.pt._{0.08} = 104°C.$

The hydrochloride, obtained by addition of ethereal hydrochloric acid to a solution of the ketone in ether, melts at 174—176°C. (from methyl ethyl ketone).

EXAMPLE 3

1 - Phenyl - 2 - pyrrolidino - 3 - methyl - butanone - (1)

35 g. of pyrrolidine in 100 ml. benzene are added with stirring at room temperature to a solution of 42 g. of α - bromo - *iso* - valerophenone in 100 ml. benzene. The reaction mixture is warmed for 2 hours at 35—40°C. and allowed to stand overnight. The product is purified as indicated under Example 1(a).

Yield: 10 g., b.pt. 126°C. (0.5 mm).

The hydrochloride melts at 225—226°C. (from acetone/ethanol).

EXAMPLE 4

(a) 1 - (4^1 - Methoxy - phenyl) - 2 - pyrrolidino - pentanone - (1)

20 g. of 1 - (4^1 - methoxy - phenyl) - 2 - bromo - pentanone - (1) ($b.pt._{0.8}$ = 156°C.) and 22.4 g. of pyrrolidine are reacted as described in Example 3. 14 g. of 1 - (4^1 - methoxy - phenyl) - 2 - pyrrolidino - pentanone - (1), $b.pt._{0.25}$ = 147°C., are obtained. Hydrochloride (colourless) m.pt. 176—178°C. (from methyl ethyl ketone).

(b) 1 - (4^1 - Hydroxy - phenyl) - 2 - pyrrolidino - pentanone - (1)

5 g. of the aminoketone obtained according to Example 4(a) are heated under reflux with 15 ml. of glacial acetic acid and 10 ml. of 70% hydriodic acid for 1½ hours. After cooling water is added and the solution shaken with ether. The ethereal layer is discarded. The solution is made alkaline with ammonia, and the separated 1 - (4^1 - hydroxy - phenyl) - 2 - pyrrolidino - pentanone - (1) is taken up in ether. After drying over sodium sulphate, the hydrochloride is precipitated with ethereal hydrochloric acid. After treatment with hot acetone, it is a colourless substance, m.pt. 250°C. Yield: 2 g.

EXAMPLE 5

1 - Phenyl - 2 - pyrrolidino - butanone - (1)

22.6 g. of α - bromo - butyrophenone ($b.pt._{0.8}$ = 98°C.) are reacted with 28.4 g. of pyrrolidine according to the method described in Example 2. 15 g. of aminoketone, $b.pt._{0.05}$ = 94°C. are obtained. Hydrochloride (recrystallised from methyl ethyl ketone) melts at 196—198°C.

EXAMPLE 6

1 - Phenyl - 2 - pyrrolidino - heptanone - (1)

27 g. of 1 - phenyl - 2 - bromo - heptanone - (1) ($b.pt._{0.3}$ = 126—132°C.) are reacted with 14.2 g. of pyrrolidine in benzene, as described in Example 2. 15 g. of 1 - phenyl - 2 - pyrrolidino - heptanone - (1), $b.pt._{0.1}$ = 136—140°C. are obtained.

The hydrochloride, (colourless crystals) melts at 158°C. (from acetone/ethanol).

EXAMPLE 7

1 - (4^1 - Chloro - phenyl) - 2 - pyrrolidino - pentanone - (1)

27.5 g. of 1 - (4^1 - chloro - phenyl) - 2 - bromo - pentanone - (1) ($b.pt._{0.2}$ = 114°C.) are reacted as described in Example 2 with 28.4 g. of pyrrolidine. 18 g. of 1 - (4^1 - chloro - phenyl) - 2 - pyrrolidino - pentanone - (1) are obtained $b.pt._{0.1}$ = 126—130°C. The hydrochloride (colourless crystals) melts at 205—207°C. (from acetone).

EXAMPLE 8

1 - (3^1 - Methyl - phenyl) - 2 - pyrrolidino - pentanone - (1)

12.5 g. of 1 - (3^1 - methyl - phenyl) - 2 - bromo - pentanone - (1) ($b.pt._{0.2}$ = 112—115°C.) are reacted with 10.5 g. of pyrrolidine as described in Example 2. 9 g. of the α-aminoketone, $b.pt._{0.15}$ = 116—118°C. are obtained. The colourless hydrochloride, recrystallised from acetone melts at 164°C.

EXAMPLE 9

1 - Phenyl - 2 - pyrrolidino - nonanone - (1)

28 g. of pyrrolidine are added with stirring to 30 g. of 1 - phenyl - 2 - bromo - nonanone - (1) ($b.pt._{0.1}$ = 138—140°C.) in 100 ml. of benzene and the mixture stirred for 4 hours at 40—50°C. The product is isolated as described in Example 1(a). 17 g. of the α-amino ketone are obtained. $b.pt._{0.1}$ = 152°C.

EXAMPLE 10

(a) Preparation of α-chlorovalerophenone

Chlorine is passed for 30 minutes into a solution of 16.2 g. of valerophenone in 150 ml. of carbon tetrachloride under illumination from a 1000 Watt lamp. The solution is heated for 40 minutes under reflux, the solvent evaporated, and the residue distilled. 13 g. of a liquid, $b.pt._{12}$ = 126—128°C., are obtained.

(b) α-Pyrrolidino-valerophenone

10.6 g. of pyrrolidine are added dropwise with stirring to 8.0 g. of α-chlorovalerophenone in 20 ml. of benzene. Stirring is continued for a further hour at 45°C. and the reaction mixture allowed to stand overnight. The product is isolated as described in Example 1(a). 4 g. of the α-aminoketone, $b.pt._{0.3}$ = 118°C. are obtained. The hydrochloride melts at 162°C. (from acetone).

EXAMPLE 11

1 - Phenyl - 2 - pyrrolidino - hexanone - (1)

18.5 g. of 1 - phenyl - 2 - bromo - hexanone - (1) ($b.pt._{0.1}$ = 108°C.) are added dropwise with stirring to a solution of 11.5 g. of pyrrolidine in 35 ml. of anhydrous benzene.

Stirring is continued for three hours. The solvent is distilled off in vacuo and the product is isolated as described in Example 1(a).

12 g. of 1 - phenyl - 2 - pyrrolidino - hexanone - (1), b.pt.$_{0.45}$ = 128—129°C. are obtained. Hydrochloride (colourless) melts at 139°C. (from acetone).

EXAMPLE 12

1 - Phenyl - 2 - (2^1 - methyl - pyrrolidino) - valerophenone

9.6 g. of α-bromovalerophenone in 20 ml. of benzene are added dropwise with stirring to 7 g. of 2 - methyl - pyrrolidine in 30 ml. of benzene. Stirring is continued for 4 hours at 40°C. and the product is isolated as described in Example 1(a). 7 g. of amino ketone are obtained, b.pt. $_{0.2}$ = 127—128°C. The colourless hydrochloride after recrystallising from ethyl acetate and from acetone melts at 133—134°C.

EXAMPLE 13—TABLETS

1 Tablet contains:—

[1 -phenyl-2-pyrrolidino-pentanone-(1)-hydrochloride]	20.0 mg.
Lactose	150.0 mg.
Potato starch	16.0 mg.
Stearic acid	4.0 mg.
Maize starch	20.0 mg.
Talc	10.0 mg.
	220.0 mg.

Preparation of 1000 tablets

20 g. of active substance, 150 g. of lactose and 13 g. of potato starch are mixed and kneaded thoroughly with a 10% aqueous slurry of the remaining potato starch and a 40% solution of the stearic acid in ethanol, passed through a screen with a mesh width of 1.0 mm and dried at 40°. The remaining auxiliary materials are admixed with the dried granulate. Tablets weighing 220 mg. are pressed from the mixture.

Tablet weight: 220 mg.

Die: 9 mm flat.

Each tablet contains 20 mg. active substance.

EXAMPLE 14—DRAGEES

1 Tablet contains:—

[1 -phenyl-2-pyrrolidino-pentanone-(1)-hydrochloride]	20.0 mg.
Lactose	140.0 mg.
Potato starch	16.0 mg.
Stearic acid	4.0 mg.
Maize starch	20.0 mg.
Talc	10.0 mg.
	220.0 mg.

Process of production

The tablets are prepared as described in Example 13.

Tablet weight: 220 mg.

Die: 9 mm, convex.

The tablets are then coated with a dragee coating containing sugar and talc. The finished dragees are polished with beeswax.

Dragee weight: 350 mg.

Each dragee contains 30 mg. active substance.

EXAMPLE 15—AMPOULES

1 ampoule contains:—

[1-phenyl-2-pyrrolidino-pentanone-(1)-hydrochloride]	10.0 mg.
Sodium phosphate sec.	5.0 mg.
Sodium chloride	14.0 mg.
Twice distilled water to	2.0 ml.

Preparation

The substances are dissolved in water under a nitrogen atmosphere and made up to the required volume with water. The solution is filtered to remove any suspended particles.

Filling: Brown, 2 ml-ampoules under nitrogen.

Sterilisation: 30 minutes at 100°C.

Each ampoule contains 10 mg. active substance.

EXAMPLE 16—DROPS

100 ml. drops contain:

1.	[1-phenyl-2-pyrrolidino-pentanone-(1)-hydrochloride]	1.5 g.
2.	Saccharin-sodium	0.2 g.
3.	Sugar	20.0 g.
4.	Methyl *p*-hydroxy benzoate	0.07g.
5.	Propyl *p*-hydroxy benzoate	0.03g.
6.	Orange Essence	0.5 g.
	Ethanol (pure)	15.0ml.
	Water (distilled) to	100.0ml.

Preparation

Substances numbered 1—3 are dissolved in about 60 ml. of water (Solution A).

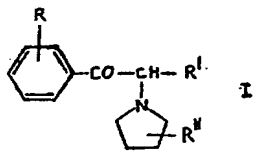
Substances numbered 4—6 are dissolved in the ethanol (Solution B).

Solution B is mixed with stirring with solution A, made up to 100 ml. with water filtered clear.

1. ml. drops contains 15 mg. active substance.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



I

(in which R represents a hydrogen atom, an alkyl or alkoxy group each containing 1 to 3 carbon atoms, a hydroxyl group or a halogen atom, R^1 represents an alkyl group containing two to eight carbon atoms and R^{11} represents a hydrogen atom or an alkyl group containing

1 to 3 carbon atoms) and non-toxic acid addition salts thereof.

2. 1 - Phenyl - 2 - pyrrolidino - butanone - (1).

3. 1 - Phenyl - 2 - pyrrolidino - pentanone - (1).

4. 1 - Phenyl - 2 - pyrrolidino - hexanone - (1).

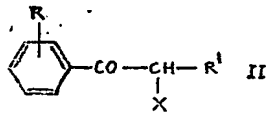
5. 1 - (4¹ - Methyl - phenyl) - 2 - pyrrolidino - pentanone - (1).

6. 1 - (4¹ - Hydroxy - phenyl - 2 - pyrrolidino - pentanone - (1).

7. 1 - (3¹ - Methyl - phenyl) - 2 - pyrrolidino - pentanone - (1).

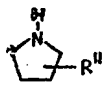
8. Salts as claimed in claim 1 formed with hydrochloric, sulphuric, phosphoric, hydrobromic, methane sulphonic, maleic, citric, tartaric acid or phthalic acid.

9. A process for the preparation of compounds of the general formula I given in claim 1 in which an α-halogeno ketone of the general formula



II

(in which R and R^1 have the meanings given in claim 1 and X represents a halogen atom) is reacted with a pyrrolidine of the general formula



III

(in which R^{11} has the meaning given in claim 1).

10. A process as claimed in claim 9 in which the condensation is carried out in the presence of an inert solvent.

11. A process as claimed in claim 10 in which the inert solvent is benzene, toluene, ether, acetone, carbon tetrachloride or chloroform.

12. A process as claimed in any of claims 9 to 11 carried out in the presence of an acid binding agent.

13. A process as claimed in claim 12 in which an excess of the pyrrolidine of general formula III defined in claim 9 is used as acid binding agent.

14. A process as claimed in claim 12 in which the acid binding agent is an organic or inorganic base.

15. A process as claimed in claim 14 in which the acid binding agent is pyridine, quinoline or an N-dialkyl-aniline or an alkali or alkaline earth metal carbonate or bicarbonate.

16. A process as claimed in claim 15 in which the acid binding agent is sodium bicarbonate or potassium carbonate.

17. A process as claimed in any of claims 9 to 16 in which the condensation is carried out at elevated temperatures.

18. A process as claimed in any of claims 9 to 17 substantially as herein described.

19. A process as claimed in any of claims 9 to 17 substantially as herein described with reference to any of Examples 1 to 12.

20. Compositions containing a compound as claimed in claim 1 together with an inert pharmaceutical carrier or excipient.

21. Compositions as claimed in claim 20 which contain between 5 and 40 mg. of a compound as claimed in claim 1.

22. Compositions as claimed in claim 21 which contain between 10 and 30 mg. of a compound as claimed in claim 1.

23. Compositions as claimed in any of claims 20 to 22 in a form suitable for oral or parenteral administration.

24. Compositions as claimed in claim 23 in the form of tablets, capsules, dragees, syrups, suspensions, solutions, elixirs, emulsions, drops or ampoules.

25. Compositions as claimed in any of claims 20 to 24 substantially as herein described.

26. Compositions as claimed in any of claims 20 to 24 substantially as herein described with reference to any of Examples 13 to 16.

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